PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* PC/00/15

Box No. I TITLE OF INVENTION

A SOMATOTROPIN COMPOSITION WITH IMPROVED SYRINGEABILITY

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

IG CHEMICAL LTD.
20, Yoido-dong, Youngdungpo-ku,
Seoul 150-721, Republic of Korea

☐ This person is also inventor.

Telephone No. 82-02-3773-3105

Facsimile No. 82-02-3773-3289

Teleprinter No.

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

This person is applicant for the purposes of: ☐ all designated States ☑ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KIM, Nam Joong
Hansin kookwha Apt. #603-301,
Samcheon-dong, Seo-ku,
Taejon-si 302-222, Republic of Korea

This person is:

☐ applicant only

☑ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☑ the United States of America only ☐ the States indicated in the Supplemental Box

☑ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☑ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHOI, Sung Min,
SHIN, Young Moo and
CHO, In Jae
Samdo Bldg. 4th Floor 1-170
Soonhwa-dong, Chung-ku,
Seoul 100-130, Republic of Korea

Telephone No. 82-02-316-4114

Facsimile No. 82-02-316-4198

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RYOO, Je Phil
Hyundai Apt. #103-504, Doryong-dong,
Yusong-ku, Taejon-si 305-340,
Republic of Korea

This person is:

- ☐ applicant only
- ☑ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: KR

State *(that is, country)* of residence: KR

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☑ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☐ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☐ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☑ **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☐ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☐ **AE** United Arab Emirates
☐ **AL** Albania .....
☐ **AM** Armenia .....
☐ **AT** Austria .....
☑ **AU** Australia .....
☐ **AZ** Azerbaijan
☐ **BA** Bosnia and Herzegovina .....
☐ **BB** Barbados
☐ **BG** Bulgaria .....
☑ **BR** Brazil .....
☐ **BY** Belarus .....
☑ **CA** Canada
☐ **CH and LI** Switzerland and Liechtenstein
☐ **CN** China .....
☐ **CR** Costa Rica .....
☐ **CU** Cuba .....
☐ **CZ** Czech Republic .....
☐ **DE** Germany .....
☐ **DK** Denmark .....
☐ **DM** Dominica
☐ **EE** Estonia .....
☐ **ES** Spain .....
☐ **FI** Finland .....
☐ **GB** United Kingdom
☐ **GD** Grenada
☐ **GE** Georgia .....
☐ **GH** Ghana .....
☐ **GM** Gambia
☐ **HR** Croatia .....
☐ **HU** Hungary .....
☐ **ID** Indonesia
☐ **IL** Israel .....
☐ **IN** India .....
☐ **IS** Iceland
☐ **JP** Japan .....
☐ **KE** Kenya .....
☐ **KG** Kyrgyzstan .....
☐ **KP** Democratic People's Republic of Korea .....
☐ **KR** Republic of Korea .....
☐ **KZ** Kazakhstan .....
☐ **LC** Saint Lucia
☐ **LK** Sri Lanka
☐ **LR** Liberia
☐ **LS** Lesotho .....
☐ **LT** Lithuania
☐ **LU** Luxembourg
☐ **LV** Latvia
☐ **MA** Morocco .....
☐ **MD** Republic of Moldova .....
☐ **MG** Madagascar .....
☐ **MK** The former Yugoslav Republic of Macedonia .....
☐ **MN** Mongolia
☐ **MW** Malawi .....
☑ **MX** Mexico .....
☐ **NO** Norway
☐ **NZ** New Zealand .....
☐ **PL** Poland .....
☐ **PT** Portugal .....
☐ **RO** Romania
☐ **RU** Russian Federation .....
☐ **SD** Sudan
☐ **SE** Sweden
☐ **SG** Singapore
☐ **SI** Slovenia .....
☐ **SK** Slovakia .....
☐ **SL** Sierra Leone .....
☐ **TJ** Tajikistan .....
☐ **TM** Turkmenistan .....
☐ **TR** Turkey .....
☐ **TT** Trinidad and Tobago .....
☐ **TZ** United Republic of Tanzania
☐ **UA** Ukraine .....
☐ **UG** Uganda .....
☑ **US** United States of America .....
☐ **UZ** Uzbekistan .....
☐ **VN** Viet Nam .....
☐ **YU** Yugoslavia .....
☑ **ZA** South Africa .....
☐ **ZW** Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....
☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

See Notes to the request form

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 24 March, 2000 (24. 03. 00)	2000-0015091	KR		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA / AT

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	4
description (excluding sequence listing part)	:	30
claims	:	3
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	38

This international application is **accompanied by** the item(s) marked below:

1. ☑ fee calculation sheet
2. ☑ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☑ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

CHOI, Sung Min
SHIN, Young Moo
CHO, In Jae

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

CHOI, Sung, Min
Samdo Bldg. 4th floor
1-170, Soonhwa-dong
Chung-gu
Seoul 100-130
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
27 April 2001 (27.04.01)	
Applicant's or agent's file reference	**International application No.**
PC/00/15	PCT/KR00/01151

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

LG CHEMICAL LTD. (for all designated States except US)
KIM, Nam, Joong et al (for US)

International filing date	:	16 October 2000 (16.10.00)
Priority date(s) claimed	:	24 March 2000 (24.03.00)
Date of receipt of the record copy by the International Bureau	:	07 November 2000 (07.11.00)
List of designated Offices	:	

EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
National :AU,BR,CA,MX,US,ZA

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [X] confirmation of precautionary designations
- [ ] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

S. Buttay

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

CHOI, Sung, Min
Samdo Bldg. 4th floor
1-170, Soonhwa-dong
Chung-gu
Seoul 100-130
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year) 14 November 2000 (14.11.00)	
Applicant's or agent's file reference PC/00/15	**IMPORTANT NOTIFICATION**
International application No. PCT/KR00/01151	International filing date (day/month/year) 16 October 2000 (16.10.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 24 March 2000 (24.03.00)
Applicant LG CHEMICAL LTD. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
24 Marc 2000 (24.03.00)	2000-0015091	KR	14 Nove 2000 (14.11.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

I. Britel

Telephone No. (41-22) 338.83.38

PCT/KR00/01151

PATENT COOPERATION TREATY

27 KP 1070

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

CHO, In Jae
7th Floor, HanJoongAng Building
#646-7, Yoksam-dong
Kangnam-ku
Seoul 135-080
RÉPUBLIQUE DE CORÉE

Date of mailing (day/month/year)
03 September 2001 (03.09.01)

Applicant's or agent's file reference
PC/00/15

IMPORTANT NOTIFICATION

International application No.
PCT/KR00/01151

International filing date (day/month/year)
16 October 2000 (16.10.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address

CHO, In Jae
7th Floor, HanJoongAng Building
#646-7, Yoksam-dong
Kangnam-ku
Seoul 135-080
Republic of Korea

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:
Appointed agent.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Idhir BRITEL

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004257760

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
CHO, In Jae
7th Floor, HanJoongAng Building
#646-7, Yoksam-dong
Kangnam-ku
Seoul 135-080
RÉPUBLIQUE DE CORÉE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 27 September 2001 (27.09.01)	
Applicant's or agent's file reference PC/00/15	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/KR00/01151	16 October 2000 (16.10.00)	24 March 2000 (24.03.00)

Applicant
LG CHEMICAL LTD. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AU,BR,CA,EP,MX,ZA

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   27 September 2001 (27.09.01) under No. WO 01/70256

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 September 2001 (27.09.2001)

PCT

(10) International Publication Number
WO 01/70256 A1

(51) International Patent Classification[7]: A61K 38/27, 31/07, 31/355

(21) International Application Number: PCT/KR00/01151

(22) International Filing Date: 16 October 2000 (16.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2000-0015091 24 March 2000 (24.03.2000) KR

(71) Applicant *(for all designated States except US)*: **LG CHEMICAL LTD.** [KR/KR]; 20, Yoido-dong, Youngdungpo-ku, Seoul 150-721 (KR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KIM, Nam, Joong** [KR/KR]; Hansin kookwha Apt. #603-301, Samcheon-dong, Seo-ku, Taejon-si 302-222 (KR). **RYOO, Je, Phil** [KR/KR]; Hyundai Apt. #103-504, Doryong-dong, Yusong-ku, Taejon-si 305-340 (KR).

(74) Agent: **CHO, In Jae**; 7th Floor, HanJoongAng Building, #646-7, Yoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

(81) Designated States *(national)*: AU, BR, CA, MX, US, ZA.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/70256 A1

(54) Title: A SOMATOTROPIN COMPOSITION WITH IMPROVED SYRINGEABILITY

(57) Abstract: The present invention relates to an improved somatotropin composition consisting of somatotropin having activity in vivo, at least one of lipid-soluble vitamins and at least one of pharmaceutically acceptable lubricants, which improves poor syringeability under cold temperature which has been a defect of the conventional somatotropin formulation using vitamins, and which shows at least the equivalent effect to that of the conventional formulation.

A SOMATOTROPIN COMPOSITION WITH IMPROVED SYRINGEABILITY

FIELD OF THE INVENTION

The present invention relates to a composition containing somatotropin having activity in vivo, and particularly, to a composition which can obtain the sustained release effect of the pharmaceutical to avoid the inconvenience of daily administration as well as have the suitable syringeability for being parenterally administered into animals to solve problems during injection, in which somatotropin is mixed with excipients.

DESCRIPTION OF THE PRIOR ART

Recently, somatotropin which can be produced in a large scale by using recombinant DNA technology according to development of genetic engineering has been commercially available for increasing the productivity of milk in cattle, and has been studied for improving feed efficiency and meat quality in swine.

Most of formulations developed hitherto for administering somatotropin having activity in vivo are simply the long acting types wherein a large amount of somatotropin is administered to avoid the inconvenience of daily administration.

For example, USP No. 5411951 and No. 5474980 disclose sustained release formulations prepared by adding a gelling agent such as aluminum monostearate into vegetable oil; by gelling the oil by heating; and by mixing somatotropin or other drugs with it homogeneously, because drugs become phase-separated and precipitated in short time when only vegetable oil is used. These techniques have been already used to prepare the sustained release formulations of various drugs such as known antibiotics(USP No. 2491537, No. 2507193 and No. 3016330), pamoate salts of oxazepines(USP No. 3676557) or relaxin which is a kind of hormone(USP No. 2964448), adrenocorticotropic hormone(USP No. 3869549), luteinizing hormone releasing factor(USP No. 4256737), gonadotropin(USP No. 3852422) and insulin(USP No. 2143590, No. 2174862, No. 2882203, No. 2920014 and No. 3102077) and the like.

There are similar prior art techniques using oil simply for preparing sustained release formulations. For example, EP 211691 discloses that somatotropin is mixed with a mixture of wax and oil and EP 213851 discloses that the sustained release formulation is prepared by mixing somatotropin with a mixture of oil and commercially available glyceride release-modifying agent. Also, EP 314421 discloses that sustained release formulations of somatotropin are prepared by adding absorption-controlling material(e.g., calcium stearate and dextran) to oil. But these are also the formulations wherein the active ingredients in the known injectable formulations containing oil used for other drugs have been substituted with somatotropin.

In addition, the sustained release techniques without using oil have been attempted. For example, in EP 193917, somatotropin was mixed with water-

soluble carbohydrate polymer(e.g., starch, dextrin) to improve the sustained release effect. However, it has shorter duration of action than formulations mixed in oil, and it may do harm on stability of somatotropin due to its water-solubility.

Different techniques from the above-mentioned techniques have been attempted for lengthening duration of action of somatotropin formulations. USP No. 4861580 discloses that the sustained release formulation of somatotropin was prepared as a liposome type by using lipid-soluble materials such as alpha-tocopherol hemisuccinate Tris salt, phosphatidyl choline and phosphatidyl ethanolamine. And in USP No. 4675189, the sustained release formulation of somatotropin was prepared as a microcapsule type by using biocompatible polymer. And in USP No. 4857506, the sustained release formulation of somatotropin was prepared as a multiple water-in oil-in water(W/O/W) emulsion type. But somatotropin formulations according to these techniques are inadequate to be commercialized since the formulations have short duration of action or very complicated manufacturing processes requiring high techniques, and low stability as well as low recovery rate of making somatotropin into a desired form.

By using quite different techniques, implantable formulations, which are solid dosage forms, were prepared for improving the sustained release of somatotropin. These techniques have been described in USP No. 4452775, No. 4761289, No. 4765980, No. 4774091, No. 4786501, No. 4863736, No. 5035891, No. 5198422, No. 5228697, No. 5356635, No. 5595752 and EP 246540 and 462959, and PCT/US92/01877, PCT/US91/08129, PCT/US90/01340, PCT/AU87/00139 and the like. These techniques tried to secure sustained

release of somatotropin by implanting somatotropin into the animal body by surgical operation using an expensive device, or implanting a compressed somatotropin form into the animal body using a special implant apparatus. These implanting techniques are preferred for obtaining a desirable release amount and sustained effect of somatotropin. However, the implanting process is too difficult to be performed on animals and animals also feel very uncomfortable due to the foreign substance.

USP No. 5520927 and Korean Patent No. 177306 attempted to lengthen duration of action of somatotropin using tocopherol acetate which has been used as an antioxidant to prevent oxidation reaction of drugs which may occur in a somatotropin composition simply containing oils as described above. However, since the viscosity of tocopherol acetate or vitamin A dramatically increases as the temperature decreases, the somatotropin composition shows such poor syringeability that cannot be used in winter or cold areas, or immediately after being taken out of a refrigerator which is the storage condition of the somatotropin composition. Thus, it needs several tens of minutes to melt the composition under ambient temperature before use. Further, the syringeability under ambient temperature is not so good that it requires the great effort and long time for injection of the composition, resulting in doubling the pain of animal being administered.

The inventors of the present invention have conducted intensive researches to solve the above-mentioned problems of conventional somatotropin formulations.

SUMMARY OF THE INVENTION

The present inventors have developed a somatotropin-containing composition which can be administered into the body by injection that is the most general administration method hitherto as well as which can be injected with superior syringeability, even in winter of dropping temperatures or immediately after being taken out of a refrigerator which is the storage condition of somatotropin composition, and which has the same or better sustained release effect and physiological activity of somatotropin as those of conventional somatotropin formulations. The composition of the present invention consists of somatotropin, at least one of lipid-soluble vitamins and at least one of pharmaceutically acceptable lubricants.

An object of the present invention is to provide a composition comprising somatotropin and vitamins with improved syringeability, which can be more easily administered into body by injection that is the most general administration method hitherto, which can decrease injection frequency resulting in reducing the labor and cost for administration as well as animals' pain, and which can increase the reproduction efficiency and the productivity of milk according to administration of somatotropin, while decrease the incidence of mastitis and metabolic diseases, by administering somatotropin with vitamins simultaneously, not separately.

Another object of the present invention is to provide a composition comprising somatotropin, which can be used in cold areas or in winter as well as immediately after being taken out of a refrigerator that is the storage condition of somatotropin composition, and which can be administered without difficulty due to of its improved syringeability under room temperature.

In accordance with the present invention, there is provided a composition consisting of somatotropin, at least one of lipid-soluble vitamins and at least one of pharmaceutically acceptable lubricants. The present invention has many advantages, including providing a composition containing somatotropin with improved syringeability. These and other features, aspects, and advantages of the present invention will become better understood with reference to the following description and appended claims.

DETAILED DESCRIPTION

The present invention provides a composition consisting of somatotropin, at least one of lipid-soluble vitamins and at least one of pharmaceutically acceptable lubricants. The present invention will hereinafter be described in more detail. The vitamins to be mixed with somatotropin in the present composition are lipid-soluble vitamins, such as vitamin A or vitamin E, which are preferred drugs in preparing a mixed formulation since they can make protein drugs such as somatotropin stable by delaying the drugs from binding with water.

In addition to the above-described advantage of the formulation, vitamin A increases the sense of vision, particularly dark adaptation in relation with rhodopsin and iodopsin, the visual dyes in rods and cones which sensitize light in the retina. It also improves abnormal dryness, degeneration, keratinization and ulceration of mucus, xerophthalmia and keratomalacia and increases the resistance against various diseases. In addition, it has been reported to be an essential element for maintenance of epithelial tissue and the growth of bone and teeth and to have a growth-stimulating activity.

Vitamin E deficiency in animals causes the white muscle disease which partly changes the color of muscle fiber into gray and makes the muscles atrophied. Initial symptoms of muscular atrophy is that the entire body loses its flexibility and appears to be stiff, and gradually becomes week and paralyzed, and then difficulty in breathing occurs. As the disease progresses, animals having severe symptoms become unable of lactation. Also, vitamin E is referred as an anti-sterility vitamin because it overcomes the sterility of animals, and it stimulates growth of animals. In addition, vitamin E helps normal reproduction processes, prevents the abnormal development of muscle and may prevent cerebromalacia, irregular activity of muscle, muscle spasm, ataxia and tonic spasm.

Hitherto, somatotropin compositions have been developed considering only the productivity and reduction of administration frequency for target animals. For example, somatotropin compositions have been designed for dairy cow, focusing on increase of the productivity of milk and reduction of the dairy farmer's labor according to the frequent administration by lengthening the in vivo duration of action of somatotropin. However, if somatotropin compositions have been administered into animals, focusing only on productivity, without considering the health conditions of animals, it may often cause side effects. The incidence of diseases such as mastitis which is a major disease of dairy cow occurs mainly due to environmental factors and hygienic factors when milking, however, it has been also reported that the incidence frequency of mastitis depends on the ability of each dairy cow. That is, it is known that mastitis more often occurs in more milk-productive cows than less milk-productive cows. Ther fore, when somatotropin is used to increase the milk productivity, proper treatment according to each cow's

milk productivity, as well as clean milking condition, is necessary to prevent the incidence of mastitis. There are many factors to cause the mastitis as mentioned above. Thus, it is preferred to increase dairy cows' resistance against bacteria as a countermeasure for prevention of mastitis. To this end, proper farm cares would be important. However, such prevention effect can be obtained by providing appropriate drugs, for example, vitamins. That is, when vitamin A or vitamin E is deficient, the mucous epithelial cells of teat canal, teat cistern and the like become keratinized, which induces the infection and proliferation of bacteria. The proliferated bacteria invade the gland cistern, resulting in severe mastitis. In addition, they lower the synthesis of immunoglobulin and keratin which are protecting materials in interior teat canal, thereby causing serious mastitis.

There are several methods for examining the mastitis, but the general method is to count the number of somatic cells in milk. The criterion for diagnosis is the number of somatic cells per 1 ml of milk, which determines level of mastitis. The lower the number, the better the milk, then the milk is recognized as having been produced from a dairy cow without mastitis.

Therefore, the present invention has prepared compositions containing somatotropin, which increase the productivity of milk, enhance the health of target animals by minimizing side effects which might be caused by the increase of milk productivity, and maximize convenience of the diary farmer who administers the compositions into animals by improving the syringeability markedly without affecting the physiological activity of the protein drug, somatotropin.

Among the lipid-soluble vitamins, particularly vitamin A may cause side effects when administered in a large amount. Thus, the formulations should be

prepared with extra care. The effects of the somatotropin and the vitamins can be maximized when an appropriate amount of the vitamins is added to the composition.

In the composition of the present invention, the pharmaceutically acceptable lubricant may be one which can be mixed with the lipid-soluble vitamins and the lubricant may be used alone or in a mixture of at least two lubricants.

The lubricants for improving syringeability of the composition which are the core of the present invention are pharmaceutically acceptable materials which do not affect the physiological activity of somatotropin. In the composition of the present invention, the pharmaceutically acceptable lubricants may include pharmaceutically acceptable alcohol or its derivatives, preferably benzyl alcohol, ethyl alcohol, isopropyl alcohol, butyl alcohol, or the like. In the composition of the present invention, the pharmaceutically acceptable lubricants also include esters of fatty acid and alcohol, such as ethyl oleate, isopropyl myristate, isopropyl laurate, isopropyl lanolate, isopropyl palmitate, or the like; unsaturated fatty acids, for example, liquid unsaturated fatty acids, such as oleic acid, linoleic acid, linolenic acid, or the like; esters of acid and aromatic alcohol, such as benzyl benzoate or the like; and other materials which can be mixed with the lipid-soluble vitamins such as polyoxyethylene alkyl ether (bridges), tetrahydrofurfuryl alcohol polyethylene glycol ether sold under the trademark GLYCOFUROL™ (c.f. "Handbook of Pharmaceutical Excipients"), derivatives of polyethylene glycol, glycerin, or the like. It is preferable that the pharmaceutically acceptable lubricant in the present invention is one which can be mixed with the lipid-soluble vitamins.

The lubricants in the present invention include pharmaceutically acceptable materials which can be well mixed with lipid-soluble vitamins, particularly vitamin A or vitamin E or derivatives thereof, to improve the syringeability. Such lubricant may be used alone or in a mixture of at least two lubricants.

Somatotropin which can be used in the composition of the present invention may be generally the somatotropin of various animals, but bovine somatotropin or porcine somatotropin is preferred. Also, in the composition of the present invention, natural somatotropin purified highly from the pituitary gland of animals or somatotropin produced artificially by recombinant DNA technology can be used.

In the composition of the present invention, the lipid-soluble vitamin may be vitamin A or its derivative, or vitamin E or its derivative. In the composition of the present invention, vitamin A or its derivative, which does not affect the physiological activity of somatotropin, for examples, any type of optical isomer of vitamin A, vitamin A acetate, vitamin A palmitate, vitamin A propionate, etc., can be used. Also, vitamin E or its derivative, which does not affect the physiological activity of somatotropin, for examples, any type of optical isomer of vitamin E, vitamin E acetate, vitamin E succinate, vitamin E nicotinate, vitamin E phosphate, etc., can be used in the composition of the present invention.

In the composition of the present invention, the somatotropin is preferably present in an amount of from 10 to 50 % by weight based on the total weight of the composition. In the composition of the present invention, vitamin A or its derivative is preferably present in an amount of from 100,000 to 5,000,000 vitamin A units and more preferably from 300,000 to 3,500,000 vitamin A units per 1 g of

somatotropin. In the composition of the present invention, vitamin E or its derivative is preferably present in an amount of from 500 to 12,000 vitamin E units and more preferably from 1,500 to 8,500 vitamin E units per 1 g of somatotropin. In the composition of the present invention, the lubricant may be preferably present in an amount of from 0.5 to 25 % by weight and more preferably from 1 to 15 % by weight, based on the total weight of the composition.

In preparing the composition of the present invention, somatotropin in a powder form may be prepared by lyophilizing a somatotropin solution alone, or by lyophilizing fine particles prepared by adding a pharmaceutical excipient(e.g., lecithin, etc.) to a somatotropin solution, or by lyophilizing the mixture of a somatotropin solution with a stabilizing agent such as sucrose, mannitol, trehalose and the like. When the lyophilized somatotropin powder is used, water content and particle size should be considered. It is preferable that the water content is 3% or below for the stability of somatotropin. The particle size which is related to phase-separation after long storage and syringeability of the composition, is preferably 10 ㎛ or below. When the particle size of the lyophilized somatotropin is bigger than the desired size, it will be necessary to carry out ball mill or air jet mill process in order to reduce the particle size, without changing the quality of the somatotropin. For example, the mixed composition of somatotropin and vitamins may be prepared by homogeneously mixing the somatotropin powder with an appropriate amount of lipid-soluble vitamins. Then, the composition of the present invention may be prepared by homogeneously mixing the mixture with an appropriate amount of pharmaceutically acceptable lubricants. Alternatively, the composition of the present invention may be prepared by homogeneously mixing

the somatotrpin with lipid-soluble vitamins and pharmaceutically acceptable lubricants. It will be apparent to those skilled in the art that the composition of present invention may be formulated into any appropriate dosage form, and may be administered in any appropriate manner.

The previously described versions of the present invention have many advantages, including providing somatotropin-containing injectable compositions with improved syringeability under the ambient temperature and cold temperature which maximize the convenience in administering somatotropin into animals' body by injection; and providing somatotropin-containing injectable compositions which can increase the reproduction efficiency and the milk productivity, while prevent the incidence of mastitis and metabolic diseases in cow and the like according to the increase of milk productivity, by administering somatotropin with lipid-soluble vitamins, particularly vitamin A, vitamin E or the like simultaneously.

The present invention will now be described in more detail in connection with the following examples, which should be considered as being exemplary only and not limiting the present invention.

EXAMPLE 1

3000 ㎖ of bovine somatotropin(LG Chemical Ltd. Biotech Research Institute) solution(130.5 ㎎/㎖) was divided into three lyophilization trays by 1000 ㎖ respectively and lyophilized in a freeze-dryer for about 48 hours. The lyophilized powder was ground using an air-jet mill to make particles of average 8 ㎛ size of diameter. Thus obtained bovine somatotropin in a powder form had

1.4 % of water content, which was measured in a heating-type moisture analyzer.

Then the lyophilized bovine somatotropin powder was homogenously mixed with vitamin E acetate(1g = 1,000 unit, ROCHE) and benzyl alcohol in a homogenizer, according to the amount described below in Table 1.

2 g of each homogenously mixed composition was taken to fill in a polypropylene syringe of 9.8 mm size of diameter having a 16-gauge needle of 1.7 cm size of length to prepare a sample for measuring syringeability. The prepared samples were stored under ambient temperature(22℃) and cold temperature(4℃) for 24 hours. The syringeability was measured by proceeding in a rate of 7.8 cm per minute using a syringeability measuring device(Test Stand Model 2252 and CPU gauge 9500 series, Aikoh Engineering, Japan) at each temperature. The measured results were shown in Table 1.

Table 1

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of benzyl alcohol (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.70	0.30	4.65	10.72
	14.25	0.75	2.86	10.01
	14.00	1.00	2.51	9.37
	13.75	1.25	2.13	7.73
	13.50	1.50	1.87	5.82
2.00	18.00	0	3.42	11.95
	16.75	1.25	1.82	5.66
8.00	12.00	0	9.04	>20
	10.75	1.25	3.23	9.99
* bST : abbreviation of bovine somatotropin				

EXAMPLE 2

Following the procedure as described in Example 1 except that isopropyl alcohol was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 2.

Table 2

Amount of *bST(g)	Amount of vitamin E acetate (g)	Amount of isopropyl alcohol (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.50	0.50	2.78	9.74
	14.00	1.00	1.83	4.67
	13.50	1.50	1.65	2.90
* bST : abbreviation of bovine somatotropin				

EXAMPLE 3

Following the procedure as described in Example 1 except that ethyl alcohol was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 3.

Table 3

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of ethyl alcohol (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.50	0.50	4.39	14.29
	14.00	1.00	2.94	12.84
	13.50	1.50	2.00	8.71
* bST : abbreviation of bovine somatotropin				

EXAMPLE 4

Following the procedure as described in Example 1 except that ethyl oleate was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 4.

Table 4

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of ethyl oleate (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.00	1.00	2.33	9.48
	13.75	1.25	2.47	7.99
	13.50	1.50	2.15	5.51
	13.00	2.00	1.70	4.07
	12.00	3.00	1.58	2.12
* bST : abbreviation of bovine somatotropin				

EXAMPLE 5

Following the procedure as described in Example 1 except that benzyl benzoate was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 5.

Table 5

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of benzyl benzoate (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.00	1.00	2.83	10.48
	13.00	2.00	2.06	7.55
	12.75	2.25	2.04	7.11
	12.50	2.50	1.98	4.79
	12.00	3.00	1.82	3.98
* bST : abbreviation of bovine somatotropin				

EXAMPLE 6

Following the procedure as described in Example 1 except that Bridge 30 was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 6.

Table 6

Amount of *bST(g)	Amount of vitamin E acetate (g)	Amount of Bridge 30 (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	12.00	3.00	1.93	4.24
* bST : abbreviation of bovine somatotropin				

EXAMPLE 7

Following the procedure as described in Example 1 except that oleic acid was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 7.

Table 7

Amount of *bST(g)	Amount of vitamin E acetate (g)	Amount of oleic acid (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	12.00	3.00	1.72	4.20
* bST : abbreviation of bovine somatotropin				

EXAMPLE 8

Following the procedure as described in Example 1 except that GLYCOFUROL™ was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 8.

Table 8

Amount of *bST (g)	Amount of vitamin E acetate(g)	Amount of GLYCOFUROL™ (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.00	1.00	3.10	9.95
	13.75	1.25	2.63	9.56
	13.50	1.50	2.28	8.61
	13.25	1.75	2.05	7.56
	13.00	2.00	2.06	5.61
	12.00	3.00	1.72	3.32
* bST : abbreviation of bovine somatotropin				

EXAMPLE 9

Following the procedure as described in Example 1 except that polyethylene glycol 400 dimethylether was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 9.

Table 9

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of polyethylene glycol 400 dimethylether (g)	Syringeability (kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.25	0.75	3.15	11.29
	13.50	1.50	2.48	6.58
	12.00	3.00	1.62	2.97
* bST : abbreviation of bovine somatotropin				

EXAMPLE 10

Following the procedure as described in Example 1 except that benzyl alcohol was used as lubricant and a mixture of vitamin E acetate and vitamin A acetate(1g = 2,800,000 IU, Sigma, U.S.A.) was used as vitamin, the composition was prepared and the syringeability was measured. The results were shown in Table 10.

Table 10

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate (g)	Amount of benzyl alcohol (g)	Syringeability (kgf)	
				Ambient temp.	Cold temp.
5.00	13.20	1.80	0	5.19	14.82
	12.60	0.90	1.50	2.16	5.61
	12.20	1.80	1.00	2.16	8.82
	11.70	1.80	1.50	2.04	5.59
	10.70	1.80	2.50	1.92	2.89
	8.35	5.40	1.25	2.06	5.64
* bST : abbreviation of bovine somatotropin					

EXAMPLE 11

Following the procedure as described in Example 10 except that benzyl benzoate was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 11.

Table 11

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate (g)	Amount of benzyl benzoate (g)	Syringeability (kgf)	
				Ambient temp.	Cold temp.
5.00	13.20	1.80	0	5.19	14.82
	11.20	1.80	2.00	2.52	9.56
	10.70	1.80	2.50	2.20	6.63
	10.20	1.80	3.00	1.83	6.29
* bST : abbreviation of bovine somatotropin					

EXAMPLE 12

Following the procedure as described in Example 10 except that a mixture of benzyl alcohol and benzyl benzoate was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 12.

Table 12

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate (g)	Amount of benzyl alcohol (g)	Amount of benzyl benzoate (g)	Syringeability (kgf)	
					Ambient temp.	Cold temp.
5.00	13.20	1.80	0	0	5.19	14.82
	11.70	1.80	1.00	0.50	2.16	6.96
	11.20	1.80	1.00	1.00	1.63	6.71
	13.00	0	1.00	1.00	1.61	5.16
	10.70	1.80	1.00	1.50	1.67	4.67
	10.20	1.80	1.00	2.00	1.53	3.43
* bST : abbreviation of bovine somatotropin						

EXAMPLE 13

Following the procedure as described in Example 10 except that ethyl oleate was used as lubricant and vitamin A palmitate(1g = 1,700,000 IU, ROCHE, Switzerland) instead of vitamin A acetate was used, the composition was prepared and the syringeability was m asured. The results were shown in Table 13.

Table 13

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A palmitate (g)	Amount of ethyl oleate (g)	Syringeability (kgf)	
				Ambient temp.	Cold temp.
5.00	12.00	3.00	0	3.56	13.86
	10.00	5.00	0	3.27	12.22
	11.00	3.00	1.00	2.01	6.23
	10.00	3.00	2.00	1.62	2.82
* bST : abbreviation of bovine somatotropin					

EXAMPLE 14

100 ㎖ of bovine somatotropin(LG Chemical Ltd. Biotech Research Institute) solution(130.5 ㎎/㎖) was mixed with 26.1 g of lecithin by using a homogenizer for 30 minutes. Then, the mixture was ground in a microfluidizer to make particles of 200 nm or below size of diameter. The suspension was filtrated through a filter of 0.22 ㎛ pore size for sterilization, transferred into one lyophilization tray and lyophilized in a freeze-dryer for about 48 hours. The lyophilized powder was ground using an air-jet mill to make particles of average 8 ㎛ size of diameter. Thus obtained bovine somatotropin in a powder form had 1.6 % of water content, which is measured in a heating-type moisture analyzer.

Using the lyophilized lecithin-bovine somatotropin powder, the composition was prepared and the syringeability was measured according to the procedure as described in Example 1 except that each amount was used as described below in Table 14. The results were shown in Table 14.

Table 14

Amount of *bST(g)	Amount of lecithin (g)	Amount of vitamin E acetate (g)	Amount of benzyl alcohol (g)	Syringeability (kgf)	
				Ambient temp.	Cold temp.
5.00	1.00	14.00	0	4.97	15.25
	1.00	12.75	1.25	2.83	10.12
* bST : abbreviation of bovine somatotropin					

EXAMPLE 15

Animal tests were carried out using the compositions prepared as described below in Table 15. Female SD rats(180~220 g) of 8-9 weeks old were used. The interval between light and darkness in a room was 12 hours, and water and feed were freely accessible. 8 rats per one composition were used and 4 rats were included in a cage for an experiment. The rats were weighed before administration of the compositions. Then, the rats were randomly separated into the treated groups, based on the average body weight and the standard error. The body weight before administration of the composition was considered as a standard body weight of each rat. 80 mg of each composition(corresponding to 20 mg of bovine somatotropin) was subcutaneously injected into the abdominal region of each rat. Then, the rats were weighed at regular time everyday for 9 consecutive days. As a control group, 8 rats without any injection were weighed during the above test period by the same method. The cumulative mean weight gain of rats of each group was indicated in Table 16, which was measured after administration of the composition.

Table 15

Composition No.	Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate (g)	Type and amount (g) of lubricant
1	5.00	15.00	0	0
2		13.20	1.80	0
3		13.50	0	Benzyl alcohol 1.50
4		11.70	1.80	Benzyl alcohol 1.50
5		12.20	1.80	Benzyl alcohol 1.00
6		14.00	0	Ethyl oleate 1.00
* bST : abbreviation of bovine somatotropin				

Table 16

		Composition No.						
		1	2	3	4	5	6	Negative control
Day	1	8.03	12.79	13.23	11.48	12.25	13.03	5.11
	2	21.51	23.06	21.56	23.18	21.80	23.20	10.48
	3	23.73	24.58	25.63	28.03	24.89	23.94	12.43
	4	26.78	28.18	27.81	32.36	33.11	28.39	9.40
	5	29.55	33.31	34.18	37.00	36.55	35.10	15.53
	6	37.79	40.95	32.76	41.46	41.59	39.20	19.93
	7	40.05	44.59	39.78	48.24	45.01	44.70	21.36
	8	35.49	40.84	38.38	44.49	44.38	40.61	19.74
	9	35.09	42.53	43.18	49.70	44.79	42.76	22.88
* Negative control : control that received no composition.								
* Unit : g								

EXAMPLE 16

Following the procedure as described in Example 15 except that compositions were prepared by mixing two kinds of lubricants as described below in Table 17, animal tests were carried out. The cumulative mean weight gain of rats of each group was indicated in Table 18, which was measured after administration of the composition.

Table 17

Composition No.	Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate(g)	Type and amount (g) of lubricant
1	5.00	13.20	1.80	0
2		11.20	1.80	Benzyl alcohol 1.00, Benzyl benzoate 1.00
* bST : abbreviation of bovine somatotropin				

Table 18

		Composition No.		
		1	2	Negative control
Day	1	10.63	10.86	1.71
	2	19.95	18.89	7.14
	3	24.08	23.45	7.45
	4	28.10	27.73	9.51
	5	32.26	33.20	13.55
	6	38.18	39.63	17.46
	7	42.44	43.09	15.64
	8	45.33	46.24	15.84
	9	43.75	44.81	19.96
* Negative control : control that received no composition. * Unit : g				

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EXAMPLE 17

Following the procedure as described in Example 15 except that compositions were prepared as described below in Table 19 with the lecithin-bovine somatotropin prepared as described in Example 14 and genetically derived dwarf female rats(90-120 g) of 8 weeks old instead of normal rats were used, animal tests were carried out. The cumulative mean weight gain of rats of each group was indicated in Table 20, which was measured after administration of the composition.

Table 19

Composition No.	Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of lecithin (g)	Type and amount (g) of lubricant
1	5.00	15.00	0	0
2		12.75	1.00	Benzyl alcohol 1.25
3		12.00	1.00	Benzyl alcohol 1.00, Benzyl benzoate 1.00
4		14.00	1.00	0
* bST : abbreviation of bovine somatotropin				

Table 20

		Composition No.				
		1	2	3	4	Negative control
Day	1	8.39	14.01	6.80	9.85	1.93
	2	12.49	17.59	13.48	11.57	3.45
	3	16.45	20.47	17.44	16.67	5.17
	4	20.25	27.63	23.58	22.87	7.37
	5	23.03	32.31	28.16	28.41	5.65
	6	28.87	35.99	31.14	31.71	8.29
	7	28.57	36.63	38.16	34.17	10.15
	8	26.21	36.19	40.56	33.55	11.61
	9	29.55	39.77	44.34	37.19	11.13
* Negative control : control that received no composition. * Unit : g						

As shown above in the Tables 16, 18 and 20, it was confirmed that the body weight of the treated group with the composition of the present invention according to the Examples 15-17, increased more than about 20 g than that of the negative control group at the 9th day after administration of the composition, the composition of the present invention had a biological effect equivalent or more to that of the composition without any lubricant, and the composition of the present invention had improved syringeability that might maximize the convenience of the diary farmer who administers the composition into animals.

Although the present invention has been described in detail with reference to the above specific embodiments, other embodiments are possible. Therefore, it should be apparent to those skilled in the art that various modifications and

changes thereof can be made without departing from the spirit and scope of the invention and that such modifications and changes be included in the scope of the following claims.

What is claim d is:

1. A composition consisting of somatotropin, at least one of lipid-soluble vitamins, and at least one of pharmaceutically acceptable lubricants.

2. The composition according to Claim 1, wherein said somatotropin is somatotropin produced by recombinant DNA technology.

3. The composition according to Claim 1, wherein said somatotropin is present in an amount of from 10 to 50 % by weight based on the total weight of the composition.

4. The composition according to Claim 1, wherein said lipid-soluble vitamin is vitamin A or its derivative, or vitamin E or its derivative.

5. The composition according to Claim 4, wherein said vitamin A or its derivative is present in an amount of from 100,000 to 5,000,000 vitamin A units per 1 g of somatotropin.

6. The composition according to Claim 4, wherein said vitamin E or its derivative is present in an amount of from 500 to 12,000 vitamin E units per 1 g of somatotropin.

7. The composition according to Claim 1, wherein said pharmaceutically acceptable lubricant is one which can be mixed with said lipid-soluble vitamins and

said lubricant is used alone or in a mixture of at least two lubricants.

8. The composition according to Claim 7, wherein said pharmaceutically acceptable lubricant is alcohol or its derivative; ester of fatty acid and alcohol; unsaturated fatty acid; ester of acid and aromatic alcohol; or other material which can be mixed with said lipid-soluble vitamins.

9. The composition according to Claim 8, wherein said alcohol or its derivative is benzyl alcohol, ethyl alcohol, isopropyl alcohol, butyl alcohol or the like.

10. The composition according to Claim 8, wherein said ester of fatty acid and alcohol is ethyl oleate, isopropyl myristate, isopropyl laurate, isopropyl lanolate, isopropyl palmitate or the like.

11. The composition according to Claim 8, wherein said unsaturated fatty acid is oleic acid, linoleic acid, linolenic acid or the like.

12. The composition according to Claim 8, wherein said ester of acid and aromatic alcohol is benzyl benzoate or the like.

13. The composition according to Claim 8, wherein said other material is polyoxyethylene alkyl ether, GLYCOFUROL, derivative of polyethylene glycol, glycerin or the like.

14. The composition according to Claim 7, wherein said lubricant is present in an amount of from 0.5 to 25 % by weight based on the total weight of the composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 00/01151

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A61K 38/27, 31/07, 31/355

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A61K 38/27, 31/07, 31/355

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/43342 A1 (LG CHEMICAL LTD.) 2 September 1999 (02.09.99) claims 1, 3-6, 8.	1-8
X	US 5520927 A (KIM et al.) 28 May 1996 (28.05.96) examples 1-12, 14, 15, 17, 20; claims 1-3.	1-4, 6-11, 13
A	WO 89/03695 A1 (NORDISK GENTOFTE A/S) 5 May 1989 (05.05.89) claim 1.	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed

„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2001 (05.02.2001)	26 March 2001 (26.03.2001)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer MOSSER Telephone No. 1/53424/437

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 00/01151

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
US	A	5520927	28-05-1996	AU	A1	70937/91	15-08-1991
				AU	B2	653325	29-09-1994
				JP	A2	4211018	03-08-1992
				JP	B2	2620417	11-06-1997
				KR	B1	9205688	13-07-1992
				KR	B1	152082	15-10-1998
WO	A1	8903695	05-05-1989	AU	A1	26160/88	23-05-1989
				AU	B2	629799	15-10-1992
				DK	A0	982/90	20-04-1990
				DK	A	982/90	22-06-1990
				EP	A1	386056	12-09-1990
				FI	A0	902042	23-04-1990
				GB	A0	8724897	25-11-1987
				JP	T2	3505406	28-11-1991
				NO	A0	901765	20-04-1990
				NO	A	901765	14-06-1990
WO	A1	9943342	02-09-1999	AU	A1	77900/98	15-09-1999
				AU	B2	716492	24-02-2000
				BR	A	9808086	08-03-2000
				EP	A1	983083	08-03-2000
				ZA	A	9805358	05-01-1999

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK88/00170

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 L 25/00, A 61 K 37/36

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC 4	A 61 L; A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as above.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A2, 0 198 213 (YEDA RESEARCH AND DEVELOPMENT COMPANY, LTD.) 22 October 1986 See page 5, line 8; example 2 & JP, 61222452	1-8,13
A	US, A, 4 526 909 (MARSHALL R. URIST) 2 July 1985 See the whole document	1-8, 13
A	US, A, 4 620 327(ARNOLD I. CAPLAN) 4 November 1986 See the whole document & WO, 86/00526 EP, 0188552	1-8, 13

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1988-12-23	1988 -01- 30
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Hans Christer Jönsson

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 9-12 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.